

REMARKS

I. Status Summary

Claims 1-3, 5-7, 9, 17-23, 26-28, 30-33, 35, 36, and 145-147 are pending and have been examined by the United States Patent and Trademark Office (hereinafter the "Patent Office") in a Non-Final Official Action dated August 4, 2009 (hereinafter the "Non-Final Official Action").

Claims 1-3, 5-7, 9, 17-22, 26, 27, 35, 36, and 145-147 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Lieber *et al.*, 1999 (73 *J Virol* 9314-9324 (hereinafter "Lieber") in view of U.S. Patent No. 6,383,794 to Mountz et al. (hereinafter "Mountz").

Claims 1 and 21-23 have also been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Lieber in view of Mountz and further in view of U.S. Patent Application Publication No. 2003/0017139 of Souza et al. (hereinafter "Souza").

Claims 1, 26-28, and 30-33 have also been rejected under this section upon the contention that the claims are unpatentable over Lieber in view of Mountz, and further in view of U.S. Patent No. 5,962,313 to Podsakoff et al. (hereinafter "Podsakoff").

Claims 59-66 and 68-142 have been canceled without prejudice. Applicants respectfully reserve the right to file one or more divisional applications with claims directed to the subject matter of the canceled claims.

Claims 1, 67 and 145 have been amended. Support for the amendment to claim 1 and 145 can be found throughout the specification as filed, including particularly at page 2, lines 25-28. Additional support can be found at page 3, lines 17-23, and at page 6, lines 14-15. The amendment to claim 67 removes the dependency from canceled claim 59. Thus, no new matter has been added by the amendments to the claims.

Reconsideration of the application as amended and based on the remarks presented hereinbelow is respectfully requested.

II. Summary of the Telephone Interview

A telephone interview was conducted on October 27, 2009. Participating in the interview were Examiner Sajjadi of the Patent Office, applicants' representatives Arles A. Taylor and Christopher P. Perkins, and applicants Andrea Amalfitano and Dwight Koeberl. Discussed during the interview was the pending rejection of the claims under 35 U.S.C. § 103(a).

In the Interview, differences between the instantly claimed hybrid vectors and the vectors described in Lieber and Mountz were discussed. Among the issues discussed was the understanding that methods described in Lieber and Mountz both result in the production of adenovirus particles.

Applicants would like to thank Examiner Sajjadi for his time and consideration in discussing the pending claims during the telephone interview.

III. Responses to the Rejections under 35 U.S.C. § 103

Claims 1-3, 5-7, 9, 12-15, 17-22, 26, 27, 35, 36, and 145-147 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Lieber in view of Mountz. Claims 1 and 21-23 have also been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Lieber in view of Mountz and further in view of Souza. Claims 1, 26-28, and 30-33 have also been rejected under this section upon the contention that the claims are unpatentable over Lieber in view of Mountz, and further in view of Podsakoff.

After careful consideration of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and submit the following remarks.

III.A. Response to the Rejection over Lieber in view of Mountz

Claims 1-3, 5-7, 9, 12-15, 17-22, 26, 27, 35, 36, and 145-147 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Lieber in view of Mountz. According to the Patent Office, Lieber describes integrating adenovirus-AAV hybrid vectors devoid of all viral genes, ITRs inserted into adenovirus (Ad) vector genomes resulting in vector genomes devoid of all viral genes, AAV ITRs flanking a reporter gene cassette inserted into the E1 region; Ad-AAV vector genomes

contain only the transgene flanked by AAV ITRs, and packaging signals, and an Ad.AAV2 hybrid vector comprising a neo gene under the control of the SV40 and Tn5 promoters. The Patent Office further contends that as the hybrid vector genome does not include coding sequence for any adenoviral or AAV proteins, it necessarily comprises deletions of the adenovirus polymerase and preterminal protein regions and does not encode AAV Rep or AAV capsid proteins.

The Patent Office concedes, however, that Lieber does not describe their hybrid virus as comprising a functional E4orf6 region. This deficiency is asserted to be cured by Mountz, which the Patent Office contends discloses high titer recombinant AAV hybrid vectors encoding a therapeutic gene flanked by ITRs of AAV and the AAV rep and cap genes, the construction of the hybrid Ad-AAV vector, by cloning the 4.2 kb Xba fragment fragment of AAV pSub201 containing the AAV rep and cap genes into the E1 Xba site of an adenoviral shuttle vector. Thus, the Patent Office contends that it would have been *prima facie* obvious for a person of ordinary skill in the art to combine their respective teachings and to include a functional adenovirus E4orf6 region in the hybrid vector of Lieber, with a reasonable expectation of success, at the time of the instant invention. The Patent Office further asserts that a person of skill in the art would construct such a hybrid adeno/AAV vector as a matter of design choice, which amounts to combining prior art elements according to known methods to yield predictable results.

Applicants respectfully traverse the Patent Office's assertion that Lieber and Mountz support a *prima facie* case of obviousness of the instant claims. Particularly, applicants respectfully submit that contrary to the Patent Office's assertion, Lieber and Mountz are not combinable because the goal in Lieber is to produce an Ad-AAV hybrid vector devoid of all viral genes, and thus one of ordinary skill in the art would not look to Mountz to "add back" any viral genes.

To elaborate, the Patent Office concedes that Lieber describes integrating adenovirus-AAV hybrid vectors devoid of all viral genes on page 6 of the Final Official Action. The deletion of all viral genes is the central goal of the Lieber reference, which states "this hybrid vector should be devoid of all Ad genes whose expression may cause immunological or toxic side effects" (see Lieber, paragraph bridging pages 9314-9315). As a result, applicants respectfully submit that Lieber teaches against a vector

comprising a functional E4orf6 region as set forth in the instant claims. Thus, and contrary to the Patent Office's assertion, one of ordinary skill in the art would not have looked to Mountz to add these viral regions to the vectors disclosed in Lieber.

Additionally, the Patent Office's assertion that a person of skill in the art would construct such a hybrid adeno/AAV vector as a matter of design choice does not support the instant rejection. It is noted that this assertion amounts to no more than an assertion that obviousness can be established merely by pointing out that the elements of a claim were known in the prior art. However, an obviousness rejection based solely on this minimal showing is specifically proscribed by the U.S. Supreme Court in *KSR International Co. v. Teleflex Inc.* (*KSR*), 550 U.S. ___, 82 USPQ2d 1385 (2007). Particularly, *KSR* stands for the proposition that "A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art" (*KSR v. Teleflex*, 127 S.Ct. 1727, 1731). The Supreme Court also stressed that "inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known" (*KSR v. Teleflex*, 127 S.Ct. 1727, 1741). Thus, applicants respectfully submit that the Patent Office's showing with respect to the instant rejection is insufficient to establish a *prima facie* case of obviousness.

Applicants submit herewith a DECLARATION OF ANDREA AMALFITANO, D.O., PH.D. PURSUANT TO 37 C.F.R. §1.132 (hereinafter "the Amalfitano Declaration"). In the Amalfitano Declaration, applicants believe they have depicted differences between the instantly claimed subject matter and the teachings of both Lieber and Mountz.

To elaborate, the instantly claimed subject matter relates *inter alia* to hybrid Ad-AAV viruses that lack pol and/or pTP. As shown in **Exhibit C** that accompanies the Amalfitano Declaration, the hybrid viruses of the presently claimed subject matter are designed to replicate in a helper cell that provides pol and/or pTP, wherein they are packaged into an Ad capsid. A hybrid virus encapsidated in an Ad capsid is then used to infect a helper cell line that expresses rep and cap in order to produce an AAV virus encoding a heterologous gene. A reference cell line, 293 cells, is recited in claims 1

and 145 for clarity. Applicants respectfully submit that the combination of Lieber and Mountz does not disclose or suggest such a hybrid virus.

Point 6 of the Amalfitano Declaration and the accompanying **Exhibit D** describe Lieber. This Point discusses that a representative method described in Lieber produces viruses that are packaged exclusively in Adenovirus capsids. More particularly, Lieber discloses a method wherein 293 cells are infected with a vector, which produces viruses that are produced are encapsidated in adenovirus capsids (see page 9315, left column, first full paragraph of Lieber). It is believed that Lieber does not disclose the production of particles encapsidated in AAV capsids.

Point 7 of the Amalfitano Declaration and the accompanying **Exhibit E** describe Mountz. As set forth therein, Mountz is believed to disclose that 293 cells are infected with a vector, which would also necessarily lead to a significant contamination with adenovirus particles. This is in contrast to the presently claimed subject matter, wherein upon infection of a helper cell line, the recombinant hybrid virus is packaged into an AAV particle essentially without producing contaminating adenovirus.

As such, applicants respectfully submit that even if one of ordinary skill in the art were to combine Lieber and Mountz as proposed by the Patent Office, the result would be that viruses encapsidated in Ad capsids would necessarily result.

Accordingly, applicants respectfully submit that the combination of Lieber and Mountz do not support a *prima facie* case of obviousness of claim 1. Claims 12-15 have been canceled, and thus the instant rejection is moot as to these claims. Claims 2, 3, 5-7, 9, 17-22, 26, 27, 35, and 36 all depend directly or indirectly from claim 1, and thus are also believed to be distinguished over the cited combination. As a result, applicants respectfully request that the instant rejection of claims 1-3, 5-7, 9, 17-22, 26, 27, 35, and 36 be withdrawn at this time.

III.B. Response to the Rejection over Lieber in view of Mountz
and further in view of Souza

Claims 1 and 21-23 have also been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Lieber in view of Mountz and further in view of Souza. The Patent Office concedes that Lieber and Mountz do not describe their hybrid AAV vectors encoding a heterologous nucleic acid as operatively associated

with a liver-specific promoter. However, the Patent Office asserts that Souza describes adeno-associated viral vectors comprising liver specific enhancer/promoter combinations linked to a transgene administered to recipient.

Applicants respectfully traverse the Patent Office's assertion that Lieber in view of Mountz and further in view of Souza supports a *prima facie* case of obviousness of claim 1. Particularly, applicants respectfully submit that Souza does not cure the deficiencies cited hereinabove with respect to the combination of Lieber in view of Mountz.

Summarily, applicants respectfully submit that Lieber in view of Mountz fails to disclose or suggest a hybrid virus that comprises Ad E4orf6 as well as a deletion of pol and/or pTP. At best, Souza discloses AAV vectors that employ different tissue-specific promoters and enhancers. However, applicants respectfully submit that Souza fails to cure the deficiency of Lieber in view of Mountz discussed hereinabove.

Therefore, applicants respectfully submit that the combination of Lieber in view of Mountz and further in view of Souza fails to support a *prima facie* case of obviousness of claim 1. Claims 21-23 all depend directly or indirectly from claim 1, and thus are also believed to be distinguished over the cited combination. As a result, applicants respectfully request that the instant rejection of claims 1 and 21-23 be withdrawn at this time.

III.C. Response to the Rejection over Lieber in view of Mountz
and further in view of Podsakoff

Claims 1, 26-28, and 30-33 have also been rejected under this section upon the contention that the claims are unpatentable over Lieber in view of Mountz, and further in view of Podsakoff. According to the Patent Office, Podsakoff describes an AAV vector comprising a gene encoding a lysosomal enzyme.

Applicants respectfully traverse the Patent Office's assertion that Lieber in view of Mountz and further in view of Podsakoff supports a *prima facie* case of obviousness of claim 1. Particularly, applicants respectfully submit that as was the case with the immediate previous rejection, Podsakoff does not cure the deficiencies cited hereinabove with respect to the combination of Lieber in view of Mountz. Particularly, applicants respectfully submit that Lieber in view of Mountz fails to disclose or suggest a

hybrid virus that comprises Ad E4orf6 as well as a deletion of pol and/or pTP. At best, Podsakoff discloses AAV vectors that encode a lysosomal enzyme. Thus, applicants respectfully submit that Podsakoff fails to cure the deficiency of Lieber in view of Mountz discussed hereinabove.

Therefore, applicants respectfully submit that the combination of Lieber in view of Mountz and further in view of Podsakoff fails to support a *prima facie* case of obviousness of claim 1. Claims 26-28 and 30-33 all depend directly or indirectly from claim 1, and thus are also believed to be distinguished over the cited combination. As a result, applicants respectfully request that the instant rejection of claims 1, 26-28, and 21-23 be withdrawn at this time.

IV. Request for Rejoinder

Certain of the claims that had been pending in the instant application have been withdrawn upon the contention that the claims are directed to unelected subject matter. Applicants respectfully request that the withdrawn claims that have not been canceled to date be rejoined to the instant application and examined at this time. Applicants further respectfully submit that the rejoined claims are believed to be patentable over the cited references for the reasons set forth hereinabove with respect to the pending rejections.

For example, the Patent Office has withdrawn claims 144 and 148. These claims recite recombinant cells comprising the claimed recombinant hybrid viruses. Applicants respectfully submit that original claim 36, which also recited cells comprising the claimed recombinant hybrid viruses, is part of the elected subject matter. Claims 144 and 148, therefore, are believed to also relate to the elected subject matter in that they include additional elements related to the cells (*i.e.*, that the recombinant cells are stably modified to express a functional pol polypeptide, a functional pTP polypeptide, or both).

As such, applicants respectfully submit that the Patent Office's assertion that claims 144 and 148 are directed to unelected subject matter is believed to be in error. Accordingly, applicants respectfully request that at least claims 144 and 148 be rejoined to the instant application and examined on the merits.

CONCLUSIONS

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any fees associated with the filing of this correspondence to Deposit Account Number 50-0426.

Respectfully submitted,

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Enclosures: Clean Version of Abstract on a Separate Sheet

Amalfitano Declaration

Exhibits B-E